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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,484	08/03/2006	David Gutig	82498	1037

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EXAMINER	
STRZELECKA, TERESA E	
ART UNIT	PAPER NUMBER
1637	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,484	GUTIG, DAVID	
	Examiner	Art Unit	
	TERESA E. STRZELECKA	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *17-20 and 23-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 21 and 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to an amendment filed November 6, 2009. Claims 1-30 were previously pending, with claims 17-20 and 23-30 withdrawn from consideration. Applicants amended claims 1-16, 21 and 22. Claims 1-16, 21 and 22 will be examined.

2. Applicants' amendments overcame the rejection of claims 1-16, 21 and 22 under 35 U.S.C. 112, second paragraph. Applicants' arguments overcame the rejection of claim 2 under 35 U.S.C. 112, first paragraph, written description. All other previously presented rejections are maintained for reasons given in the "Response to Arguments" below.

Response to Arguments

3. Applicant's arguments filed November 6, 2009 have been fully considered but they are not persuasive.

A) Regarding the rejection of claims 1-13 under 35 U.S.C. 1029b) as anticipated by Bransteitter et al., Applicants argue that Bransteitter et al. do not teach the step of c) of claim 1, i.e., "concluding, from the presence or the proportion of deaminated positions, the methylation status of the DNA to be investigated in said positions".

However, it is very clear from the legend to Fig. 1 that this is what Bransteitter et al. do. The legend to Fig. 1 (a) states: "Assay 1 detects dC deamination by using UDG and APE.". Therefore, the fact that there is a result indicating deaminated cytosine is a conclusion that the methyl group was present on that cytosine. Therefore this limitation is anticipated.

B) Regarding the rejection of claims 12-16, 21 and 22 under 35 U.S.C. 103(a) over Bransteitter et al. and Olek et al., Applicants argue that:

"Because Bransteitter explicitly states that deamination efficiencies were calculated from extension reactions with ddA mix or from extension reactions with ddG mix, a person of ordinary

skill in the art would have considered the use of such ddA mix or ddG mix as necessary for detecting deamination of cytosines, i.e., converted uracils.

For this reason, even if a person of ordinary skill in the art would have had the idea of combining the method of Bransteitter with the method of Olek, he would have ended up with a method wherein said ddA or said ddG mixes are used for primer extension, irrespective of whether this primer extension is a single extension or part of a PCR, real-time PCR or conducted in the presence of blocking oligonucleotides. However, according to the claimed method, a primer extension is not necessary. According to step (b) of claim 1, the sequence of partially deaminated DNA is analyzed. According to claim 12 (as well as claims 13-16 dependent therefrom), such analysis may comprise amplification, preferably a polymerase mediated amplification, more preferably by means of PCR, and most preferably either in the presence of methylation-specific primers or a methylation specific blocker oligonucleotide. In contrast to the teaching of Bransteitter and thus in contrast to a combination of Bransteitter and Olek, the use of a mixture of three dNTPs with either ddA or ddG is not necessary."

One of ordinary skill in the art would have clearly understood that the amplification method of Olek et al. is not to be combined with the elongation method of Bransteitter et al., but rather that it is a substitute for it.

The rejection is maintained.

Claim Rejections - 35 USC § 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

5. Claims 1-13 are rejected under 35 U.S.C. 102(a) as being anticipated by Bransteitter et al. (PNAS USA, vol. 100, pp. 4102-4107, April 2003; cited in the IDS).

Regarding claim 1, Bransteitter et al. teach a method for the detection of cytosine methylation in DNA (Abstract) comprising the steps of:

a) bringing the DNA to be investigated into contact with a cytidine deaminase, whereby the cytidine deaminase deaminates cytidine and 5-methylcytidine at different rates (page 4102, paragraphs 3-5),

b) investigating the partially deaminated DNA with respect to its sequence (page 4102, last paragraph; page 4103, first and second paragraph), and

c) concluding from the presence or the proportion of deaminated positions the methylation status of the DNA to be investigated in said positions (Fig. 1; Fig. 2).

Regarding claim 2, Bransteitter et al. teach AID (page 4102, fourth paragraph).

Regarding claims 3 and 4, Bransteitter et al. teach single-stranded and partially-single stranded DNA (page 4102, third paragraph; Table 1).

Regarding claims 5-7, Bransteitter et al. teach single stranded regions being between 3 and 20 nucleotides long, between 5 and 12 nucleotides long and 9 nucleotides long (Table 1, page 4106).

Regarding claims 8 and 9, Bransteitter et al. teach oligomers between the length of 20 to 150 nucleotides and 35-60 nucleotides (Table 1, page 4106).

Regarding claims 10 and 11, Bransteitter et al. teach oligomers concentration of 100 nM (page 4102, fifth paragraph), anticipating the claimed ranges.

Regarding claims 12 and 13, Bransteitter et al. teach amplification of the deaminated fragment using a polymerase (page 4103, second paragraph).

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 12-16, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bransteitter et al. (PNAS USA, vol. 100, pp. 4102-4107, April 2003; cited in the IDS) and Olek et al. (U.S. Patent No. 7,229,759 B2).

A) Bransteitter et al. teach detection of the converted uracil residues using primer extension and ddA, but do not teach PCR or real-time PCR or using blocker oligonucleotides in the amplification reaction.

B) Regarding claims 12-14, 21 and 22, Olek et al. teach detection of deaminated cytosines resulting from bisulfite reaction using real-time PCR (col. 5, lines 37-53; col. 13, lines 45-59).

Regarding claim 15, Olek et al. teach methylation-specific primers (col. 2, lines 56-67; col. 3, lines 1, 2; col. 11, lines 15-31).

Regarding claim 16, Olek et al. teach using blocking oligonucleotides during amplification (col. 6, lines 3-20 and 38-67; col. 11, lines 29-49).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used the amplification methods of Olek et al. with blocking oligonucleotides to detect the converted cytidines in the method of Bransteitter et al. The motivation to do so is provided by Olek et al. (col. 13, lines 52-59 and col. 11, lines 67 and col. 12, lines 1-3):

"A particularly preferred variant of the method, however, is the simultaneous detection of qualifier positions and classifier positions in one experiment, which can be achieved by the use of TaqMan or LightCycler technology variants. Additional fluorescently labeled oligonucleotides are to be added to the oligonucleotides, which provide for a preferred amplification of the DNA to be investigated, and the change in fluorescence is measured during the PCR reaction. In principle, since the DNA to be investigated is amplified, information on the methylation status of different classifier CpG positions is obtained predominantly also directly from this change in fluorescence. Since different oligonucleotides are each preferably provided with different fluorescent dyes, a distinction of the change in fluorescence during the PCR is also possible, separately for different positions."

"If only one small group of CpGs is available and still a high amount of background DNA has to be blocked, it is therefore preferred that one part of this group of CpGs is covered by a methylation specific primer and the other part is covered by a methylation specific blocking probe, and the binding site of this non-extendible probe could ideally even overlap with the binding site of the primer. This way, high relative sensitivity, this means highly preferred amplification of the DNA to be analyzed while suppressing the background DNA, can be achieved with only a small group of CpGs as Qualifier positions."

8. No claims are allowed.

Conclusion

9. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TERESA E. STRZELECKA whose telephone number is (571)272-0789. The examiner can normally be reached on M-F (8:30-5:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Teresa E Strzelecka
Primary Examiner
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/Teresa E Strzelecka/
Primary Examiner, Art Unit 1637
January 13, 2009